



## Recognizing Clonorchiasis: A Foodborne Illness Leading to Significant Hepatobiliary Disease

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Clonorchiasis, known as the Oriental liver fluke, is implicated in a wide spectrum of hepatobiliary disease ranging from asymptomatic infection to more severe liver disease including cholangitis or portal hypertension. It is a foodborne zoonosis caused by the consumption of undercooked or raw fish contaminated with the parasite *Clonorchis sinensis*. There are estimated to be at least 15 million cases of clonorchiasis worldwide, contributing to approximately 5600 deaths in 2005.<sup>1,2</sup> The disease has a predilection for males over females and for individuals of increasing age, with the highest rate in those aged 50 to 59 years old.<sup>2</sup> The overwhelming majority of cases occur in endemic areas in eastern Asia, including China, Hong Kong, Vietnam, Korea, and eastern parts of Russia.<sup>1</sup> Cases of clonorchiasis in other parts of the world typically involve infections in immigrants from, or travelers to, endemic countries, or those who have eaten freshwater fish imported from endemic areas.

Clonorchiasis was originally described in 1874 by a pathologist who observed a new species of liver fluke in the bile ducts of a Chinese man during autopsy.<sup>3</sup> The causative agent was identified as *Clonorchis sinensis*, a helminth transmitted by the ingestion of raw or inadequately cooked freshwater fish. Figure 1 depicts the life cycle of this liver fluke involving two intermediate hosts before reaching its definitive host. Piscivorous mammals, including humans, dogs, and cats, are the definitive hosts, in which sexual reproduction takes place. These hosts acquire the parasite by ingestion of freshwater fish contaminated with metacercariae, the infective form. In the intestines, the metacercariae excyst and migrate to the biliary ducts, where they mature into the adult form. Each adult fluke lays approximately 2500 to 3000 eggs every day that are passed in the

stool and taken up by freshwater snails. Snails are an intermediate host in which asexual reproduction occurs and the parasite develops into free-swimming cercariae. Burrowing out of the snail, the motile cercariae encyst onto the scales or within the muscles of the second intermediate host, freshwater fish. The parasite's longevity means that *C. sinensis* can live more than 25 years within its human host.<sup>3-5</sup>

A disease with protean clinical manifestations, severity of infection with *C. sinensis* is determined in large part by the degree of worm infestation.<sup>6-8</sup> Low worm burden can lead to mild infection with no or few symptoms, such as general malaise, abdominal discomfort, and diarrhea, whereas moderate or severe infection with heavier worm burden can precipitate systemic illness with fever, chills, anorexia, and abdominal pain and the development of chronic infection leading to hepatobiliary disease. Manifestations of severe disease can include cholecystitis, cholangitis, or portal hypertension leading to hepatosplenomegaly and ascites. Biliary obstruction from adult worms leads to complications such as pyogenic cholangitis, liver abscess, hepatitis, and pancreatitis.<sup>6-8</sup> Importantly, chronic infection with *C. sinensis* has been associated with biliary hyperplasia leading to periductal fibrosis and ultimately has been linked to the development of cholangiocarcinoma (Fig. 2). The causative role for clonorchiasis in this malignancy is supported by several epidemiological studies, leading to the recognition of *C. sinensis* as a carcinogen by the International Agency for Research on Cancer in 2009.<sup>2,7</sup>

Diagnosis of clonorchiasis is challenging. It should be clinically suspected in patients who present with biliary disease and have the relevant epidemiologic risk factors. There are no pathognomonic laboratory values, although patients

Abbreviation: CT, computed tomography.

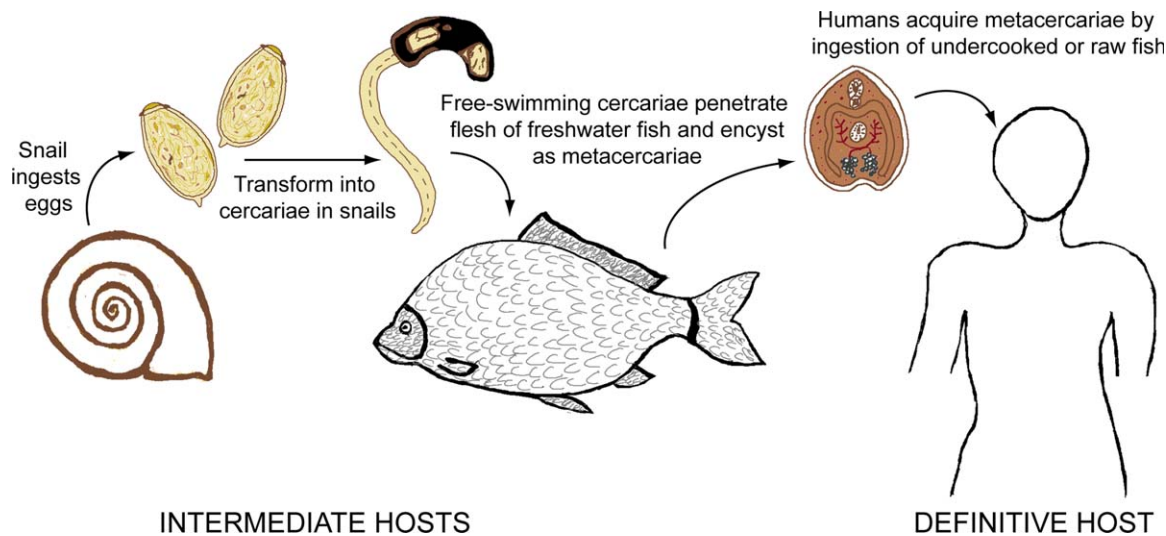
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**Figure 1** The life cycle of *Clonorchis sinensis* involves two intermediate hosts, snails and freshwater fish, before the trematode reaches its definitive host, which includes humans.



**Figure 2** Representative CT image of patient with cholangiocarcinoma presumed secondary to clonorchiasis. Note the presence of a large, lobulated central hepatic mass with associated intrahepatic biliary ductal dilation.

may have peripheral eosinophilia, elevated transaminases, and elevated cholesterol levels.<sup>7</sup> Definitive diagnosis is primarily based on the detection of *C. sinensis* eggs on fecal examination.<sup>7-10</sup> Microscopic detection of eggs in duodenal aspirates can be highly sensitive but is infrequently performed because collection of duodenal fluid requires an invasive procedure. Serological tests such as antibody detection with ELISA can support the diagnosis, but cannot distinguish between acute and past infection.<sup>6</sup> Multiple imaging modalities used to evaluate the extent of hepatic or biliary disease can further help confirm the clinical diagnosis.<sup>7,10</sup> Although ultrasonography can be used to detect adult flukes in the biliary system in cases of heavy worm burden, conventional cholangiography and endoscopic retrograde cholangiopancreatography are more sensitive at

detecting filling defects in bile ducts due to the presence of adult flukes. There are other features on imaging that may support a diagnosis of clonorchiasis. Diffuse, uniform, and mild dilation of distal intrahepatic bile ducts in the absence of extrahepatic biliary dilation on ultrasound or computed tomography (CT) is suggestive of clonorchiasis.<sup>7,10</sup>

The treatment of choice is the antihelminthic drug praziquantel, with reported high cure rates (83%-98%) in endemic areas.<sup>5,6,9,10</sup> It is well tolerated, with mild adverse effects limited to headache, dizziness, or abdominal discomfort. Albendazole, another antihelminthic agent, also has been used successfully to treat clonorchiasis.<sup>5,7</sup> Praziquantel is typically administered in divided doses for one to three days for complete eradication, although single-dose regimens have been used in mass treatment campaigns with effective reduction in the prevalence of disease in endemic countries.<sup>7</sup> Given the direct medical and indirect economic losses associated with *C. sinensis* infection, there is a need for multifaceted prevention programs in addition to chemotherapeutic approaches. Highlighting the risk of infection with ingestion of cultural delicacies composed of raw or undercooked seafood, education campaigns have been effective in helping change traditional ways of preparing fish.<sup>7</sup>

Recognized as a neglected tropical disease by the World Health Organization, clonorchiasis imparts substantial health and economic costs on the world's poorest populations. Because patients typically do not seek medical attention until late in the disease course, often presenting with life-threatening sequelae, intensive education and prevention programs to control and halt transmission of clonorchiasis in endemic countries are urgently needed. Healthcare providers can support these efforts by considering this clinical entity in



the differential for hepatobiliary disease in patients with relevant epidemiological risk factors.

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